(2) an amount of a second active ingredient (b), said second active ingredient (b) being atorvastatin or a pharmaceutically acceptable salt thereof;

wherein said first active ingredient (a) and said second active ingredient (b) are each administered together with a pharmaceutically acceptable carrier or diluent.

151. (Amended) A method of treating atherosclerosis in a mammal which has been examined for atherosclerosis by a medical practitioner and diagnosed as in need of therapy for said atherosclerosis by the joint administration of the active ingredients designated as (a) and (b) below, which comprises administering to said mammal

(1) an amount of a first active ingredient (a), said first active ingredient (a) being amlodipine or a pharmaceutically acceptable acid addition salt thereof; and

(2) an amount of a second active ingredient (b), said second active ingredient (b) being atorvastatin or a pharmaceutically acceptable salt thereof;

wherein said first active ingredient (a) and said second active ingredient (b) are each administered together with a pharmaceutically acceptable carrier or diluent.

Remarks

Upon entry of the Supplemental Amendment, the claims will be 1 – 3, 84 – 101, 106, 109, 112, 115, and 118 – 184. The claims pending in the Application that read on the elected species within invention VII include those set forth in the Amendment of October 25, 2001 at page 6. Applicants wish to inform the Examiner that claims 121 – 131 also correspond to invention VII and the elected species. Therefore, Applicants believe that pending claims 99 – 101, 106, 112, 120 – 144, and 173 – 180 should be acted on by the Examiner.

Applicants have amended the pending claims to remove the language "optionally and independently". This language was discussed at the Interview held on October 24, 2001 as possibly confusing. As written, the language was intended to encompass both fixed combinations of (a) and (b) (in a single dosage form) or free combinations ((a) and (b) in separate dosage forms), in each instance together with a diluent or carrier. The claims, as amended, encompass the same subject matter. Applicants have simply removed the language from the pending claims in an effort to further prosecution, without a change in scope.

Applicants respectfully direct the Examiner's attention to the discussions at pages 24-25 and 28 of the Remarks section of the previous amendment relating to the Sever paper relied upon by the Examiner. The Sever article describes the state of the art specifically directed to the field of Applicant's elected invention. Sever concludes that further trials are needed to answer remaining questions including what are the benefits, if any, of joint therapy. At best, Sever, who does not identify the claimed combination, supports the uncertain state of the art and provides no motivation to select the two specific active ingredients for the claimed method of treatment. Especially when considered with the other literature, Sever firmly shows that the totality of the art supports at best "obvious to try", and not obviousness under §103. *See* previous Amendment at pages 24 – 25 and 28 – 29.

Applicants also wish to draw the Examiner's attention to the fact that atorvastatin was commercialized by Warner-Lambert around February of 1997. This is within a year of Applicants' effective filing date. A prior art issue may arise from the commercial sale of atorvastatin for the reasons similar to those set forth in the discussion of the Warner-Lambert clinical trials. *See* Amendment at pages 6 – 10. But if such occurred, it is not a statutory bar to

the instant claims, and in any event the claims distinguish over such chance event even were it deemed to be prior art.

In summary, claims 99-101, 106, 109, 112, 115, and 120 are drawn to methods wherein the recited amlodipine and atorvastatin (and salts) are administered together in a single pharmaceutical composition. Claims 173, 175, 177, 179, 181 and 183 are similarly limited to administration of a single pharmaceutical composition in methods that are narrower than the method of claim 99. Such claims clearly distinguish over any chance administration of the two ingredients separately such as in the Warner-Lambert trials, even assuming such trials were prior art. The remaining claims, while generic to fixed and free combinations, distinguish over, for example, the Warner-Lambert trials by the method steps recited. *See* Amendment at pages 10-12. All claims distinguish over the "obvious to try" references for the reasons discussed above and in the previous remarks.

For the convenience of the Examiner, Applicants are submitting an unmarked version of all the pending claims with this Amendment.

A prompt and favorable response is earnestly solicited. If the Examiner believes that further discussion, face-to-face or by telephone, would advance the prosecution, please contact the undersigned.

Respectfully submitted,
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